

REMARKS

Claims 14, 15 and 19 are active in the present application. Support for the amendment to the specification is found on page 35, lines 10-11. Support for the amendment to the claims is found in Claims 17 and 18 and the specification as originally filed. No new matter is added. Favorable reconsideration is respectfully requested.

The present invention provides a method for preparing a vaccine against human immunodeficiency virus by introducing into a vector DNA or liposome a nucleic acid encoding an envelope glycoprotein of HIV wherein said envelope glycoprotein comprises a deletion of the third variable loop (V3) and mixing said vector DNA or liposome with a suitable adjuvant (see Claim 14) and a vaccine for inducing cellular immunity (see Claim 19).

The rejection of Claims 1-13 under 35 U.S.C. §102(b) over Chada et al is obviated by the cancellation of these claims.

The rejection of Claims 1-20 under 35 U.S.C. §112, second paragraph is obviated by amendment.

Claims 1-20 are rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which is not adequately described in the specification to convey to the skilled artisan that the inventors had possession of the invention at the time of filing. It is submitted that this ground of rejection is unsustainable in view of the foregoing amendments and the following remarks.

The Examiner asserts that the specification allegedly does not describe the construction of the various V3 mutants (see pages 2-4 of the Official Action). However, Applicants point out that the specification on page 26 describes the construction of the vv- Δ V3 mutant with the Δ 297-329 deletion as described in Wyatt et al (reference 15, which is

also referred to on page 35, lines 10-11). In addition, the specification provides full and complete description of construction of each of the V3 mutants as described in the Examples on page 26, Example 2; page 35, lines 1-13 and the references cited therein. Specifically, with respect to the 1ΔV3, 7ΔV3 and 8ΔV3 mutants and WTP-2, WTP-5 and WTP-8, the 1ΔV3, 7ΔV3 and 8ΔV3 mutants are clones comprising a deletion in the env glycoprotein (V3 loop deletions) and the WTP-2, WTP-5 and WTP-8 clones are wild-type env glycoproteins. It is submitted that the construction of the various mutants and clones are described in the specification and thus provides adequate guidance to the skilled artisan to make and/or use the claimed invention. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claims 1-20 are also rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which is not enabled in the specification. It is submitted that this ground of rejection is unsustainable in view of the foregoing amendments and the following remarks.

The Examiner agrees that "the specification provides CTL and antibody-dependent cell-mediated cytotoxicity data *in vitro* (pages 35-38)" and asserts that the invention is not enabled because the specification "does not provide any examples of inducing cellular immunity *in vivo* or provide adequate correlative evidence between *in vitro* data and *in vivo* results such that a therapeutic or prophylactic effect against a virus could be obtained" (See pages 7-8 of the Official Action). Further, the Examiner asserts that *in vitro* CTL data is not predictive of *in vivo* results in view of several references authored by Ross, Verma etc. (see pages 5-7 of the Official Action). Thus, the Examiner asserts that the *in vitro* CTL data do not correlate with *in vivo* protective efficacy.

Applicants respectfully disagree and point out that contrary to the scientific

publications which the Examiner cites in support of his position, it is submitted that the skilled artisan would recognize that *in vitro* CTL data does correlate with *in vivo* protective efficacy. As illustrations of the knowledge in the art of such correlation, Applicants submit herewith three references (Johnson et al, Daniel et al and Wyand et al). The data in these three publications clearly show that vaccination of juvenile and adult Rhesus monkeys with SIVmac239 Δ nef (deficient in nef) and SIVmac239 Δ 3 (deficient in nef, vpr and upstream sequences in U3) resulted in induction of a vigorous CTL response (see Johnson et al) and protected the animals against challenge by intravenous inoculation of live, pathogenic SIV (see Daniel et al and Wyand et al).

Furthermore, the specification teaches modifying immunodominant epitopes (see, for example, pages 1-3 and 23) in view of the disadvantage of vaccines which maintain an unmodified immunodominant epitope (e.g., V3 region as described on pages 2-3).

Accordingly, it is submitted that the specification reasonably conveys to one of skill in the art that the specification fully enables the instant claims. In view of the foregoing, Applicants respectfully request withdrawal of this ground of rejection.

The objection to the specification is believed to have been obviated by appropriate amendment.

Applicants submit that the present application is now in a condition for allowance.

Early notification of such is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Norman F. Oblon
Attorney of Record
Registration No. 24,618

Daniel J. Pereira, Ph.D.
Registration No. 45,518



22850

(703) 413-3000
Fax #: (703) 413-2220
NFO:DJP\cct

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IN THE SPECIFICATION

Page 26, replace the text beginning at line 12 with the following paragraph:

--The HIV-1IIIB isolate was the source of the full-length env gene and the $\Delta V3$ loop mutant cloned in the pSCII-based vector under the control of a synthetic early/late vv promoter (Earl et al, 1990, Removal of cryptic poxvirus transcription termination signals from the human immunodeficiency virus type 1 envelope gene enhances expression and immunogenicity of a recombinant vaccinia virus. *J Virol.* 64:2448-2451). The vv- $\Delta V3$ mutant with the $\Delta 297-329$ deletion ([15] Wyatt, R.M. et al, *J. Virol.* 66:6997-7004, incorporated by reference herein in its entirety) was constructed by ligation of fragments obtained by PCR amplification from the pSVII-env plasmid (a gift from Dr. J. Sodroski, Dana-Farber Cancer Institute, Boston, MA). One fragment was generated by PCR with the synthetic oligonucleotide containing the *SaI* site and the CCACC Kozak's sequence in front of the ATG codon (5'-AGAGTCGACCCACCATGAGAGTGAAGGAGA-3', sense) (SEQ ID NO:1), and the oligonucleotide (5'-ACAGGTACCCCATAGACTGTGAC-3' antisense) (SEQ ID NO:2) containing the *KpnI* site, used for ligation with the second env fragment. The second fragment was derived by *KpnI* and *BamHI* digests of the pSVIII-env plasmid, and the third fragment was generated by PCR with the synthetic oligonucleotide containing the *BamHI* site at its 5' end (5'-AACGGATCCTTAGCACTTATCTGGG-3', sense) (SEQ ID NO:3) and the antisense primer (5'-TTGCGCGGCCGCTTATAGCAAAATCCTTTCC-3') (SEQ ID NO:4) containing the TAA

stop codon followed by the *NotI* site. The three fragments were ligated into the *SaII* and *NotI* sites of the pSC11-based vector (a generous gift of Dr. L. Eisenlohr, Thomas Jefferson University, Philadelphia, PA) to generate plasmid pSC-ΔV3. A similar approach was used to generate plasmid with the WT env gene (pSC-WTP) using recombinant clone pIIIB (Hwang, et al, *Science* 253:71-74) kindly provided by Dr. B. Cullen (Howard Hughes Medical Institute, Duke University Medical Center, Durham, NC). Plasmids pSC-ΔV3 and pSC-WTP were used to generate vv-ΔV3 and vv-WTP by homologous recombination as described (Earl et al, 1990, *J Virol.* 64:2448-2451).--

IN THE CLAIMS

Claims 1-13 (Canceled).

--14. (Amended) A method for preparing a vaccine against [a virus] human immunodeficiency virus (HIV) comprising:

(a) introducing into a vector DNA or liposome a nucleic acid encoding an envelope glycoprotein of [said virus] HIV, wherein said envelope glycoprotein [contains a modified immunodominant epitope] comprises a deletion of the third variable loop (V3); and

(b) mixing said vector DNA or liposome with a suitable adjuvant.

15. (Amended) The method of Claim 14, wherein said nucleic acid is introduced into [APCs] antigen presenting cells (APCs) and said APCs are mixed with adjuvant.

Claims 16-18 (Canceled).

19. (Amended) A vaccine for inducing cellular immunity against [a virus] HIV comprising:

(a) cells expressing on their surfaces an envelope glycoprotein of HIV [said virus], wherein said envelope glycoprotein [contains a modified immunodominant epitope]

comprises a deletion of the third variable loop (V3); and

(b) an adjuvant.

20. (Canceled).--